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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,326	GRONTHOS ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *172,175-181 and 183-194* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *172,175-181 and 183-194* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/13/09; 06/05/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 05/26/2009 in response to office action mailed on 11/13/2008 has been acknowledged.

Claims 172, 175, 177-179, 184, and 187-191 are amended.

Claims 131-171, 173,174, and 182 are canceled.

Claims 192-194 are new.

Claims 172, 175-181 and 183-194 *are pending and are examined in this office action. Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.*

Applicants arguments in the response filed on 05/26/2009 are fully considered while writing this action.

Withdrawn: Claims 172, 175-181 and 183-191 are rejected under 102(b) as being anticipated by Chopp et al., (2002, The Lancet Neurology 1:92-100) for the reason of record as set forth in the office action mailed on 11/13/2008 is withdrawn in view of Applicants amendments and arguments and further in view of the revised 35 USC 103 rejection below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 172, 175-181, 183-192 and 193-194 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing neovascularization at the site of administration by administering to the target tissue of an effective amount of mesenchymal precursor cells (MPCs) derived from bone marrow that express STRO-1, does not enable any Stro1+ cells, does not enable repair of blood vessel in any tissue, does not enable any routes of administration of said Stro1+ MPCs,

and does not enable therapy of any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims as explained below for the reasons of record as set forth in the office action mailed on 11/13/2008.

Response to Applicants Arguments in the Response of 05/26/2009:

The Applicants amends claims and argues that the scope of enablement rejection of the instant claim should be withdrawn because, the Applicant argues, that the prior art is not unpredictable regarding MPCs/MScs based cell therapy for vascular repairs or angiogenesis. The Applicant further argues that the sMPCs/MSCs could administered by any routes for repairing an injured blood vessel in any target tissue or inducing angiogenesis in any target tissue.

The Applicants arguments are however found not persuasive because of the ambivalence of the Applicant with regard to Stro1+ cells used in this invention. On one the Applicant hand argues that the instantly claimed Stro-1+ cells are distinct from "standard" MPCs/MSCs known in the art of BM cell therapy whlw at the same time completely or heavily leaning on the prior art on "standard" BM derived MPC/MSCs cell therapy in support of the enablement of the instantly claimed broad use of Stro1+ cells. Applicant should note that, even providing that the "standard" MSCs/MPCs of the prior art did comprise effective amount of Stro 1+ cells, the art is still unpredictable regarding treating any disease or any injury involving blood vessels in any tissue. Only relatively well understood source MPCs/MSCs of clinically meaningful angiogenesis induction, at the time of instant invention, were bone marrow or bone marrow derived MSCs/MPCs and/or especially the isolated bone marrow derived, culture expanded CFU-F progenies. All of the above sources apparently comprised multiple cell types of MPCs including Stro1+ expressing MPC cells. Further the use of any Stro 1+ cells, as instantly claimed, will not do because the art clearly teaches that all Stro1+ cells are not MPCs or MSCs (that have a potential to differentiate into different cell types). For example Simmons et al (1991, Blood 78:55-62; art of record) clearly teaches that 95% of BM derived Stro 1+ cell are nucleated erythroid cells and are apparently not the progenitor cells (see p.57, Table 4, supra; p.58, col.1 and Table 3). Thus stro1+ MPCs

account for only a small percentage of BM derived Stro1+ cells. In this back ground of unpredictability in the art, it is incumbent upon the Applicant to provide enabled examples to support the broad claims of using any route of administration and using of any Stro 1+ cell and from any tissue source. The as filed specification however, fails disclose sufficient number of enabled examples to support broad claims to different routes of administrations (the only example being the induction of arterioles at the site of injection of said Stro 1+ cell comprising MPCs to tumor transplants or hearts of athymic nude rats (paragraph 0137-0140)) or broadly claimed use of any stro1+ cell from any tissue source (the only example being the use of MPCs derived from bone marrow that comprised stro1+MPCs). The specification as filed further does not provide support for the broad claims to using MPCs from a laundry list of animal tissue sources in claimed in claim 184. Thus because of the upredictability in the relevant art regarding MPC/MSC based cell therapies in general and sparse support for the use of Stro1+ cells in particular as indicated in the previous office action combined with the scant support for the use of the same as enabling disclosures in the as filed specification, it would have been "undue experimentation" for the artisan to make and use the claimed invention in its full scope. Hence the enablement rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 172, 175-181 and 183-194 are rejected under 103(c) as being unpatentable over Chopp et al., (2002, The Lancet Neurology 1:92-100; art of record) in view of Jones et al (2002, Arthritis and Rheumatism 46:3349-3360; art of record), Bianco et al (2001, Stem cells 19:180-192) and Dennis et al (2002, Cells Tissues Organs 170:73-82)

The above The claims are drawn to a method of inducing formation or repair of blood vessels by administering via any route an enriched population of isolated and cultured cells that express the marker STRO-1 wherein in further limitations the cells used express STRO-1 are mesenchymal precursor cells (MPCs) that are enriched to variable extent, comprise additional markers 3G5, MUC18/CD46 and/or alpha smooth muscle actin and/or negative for certain other markers, derived from several different tissue sources, isolated from different niches from a tissue and preferably from perivascular niche and enriched to different extent with respect to cells possessing said markers.

Regarding claims 172, 175-181 and 183-191 Regarding the claim limitations of vasculogenesis or neovascularisation using MSCs (MPCs) Chopp teaches a method of promoting angiogenesis during a treatment of neural injury with bone marrow stromal cell including mesenchymal stem cells (MSC) following in vivo and systemic administration of said cells in rats (entire article; abstract; p.93, col.1 2nd paragraph bridging col.2). Chopp further teaches their in vitro expansion and direct implantation, injection as well as systemic administration of said cells including intravenous delivery and effect the recovery from pathological process by regenerative angiogenesis, vasculogenesis (Abstract; p.96-98; Fig.3). Stro-1 marker expression in said MSC is inherent for these fibroblastic bone marrow cells and it was known in the art at the time of invention. Chopp however, does not expressly teach various claimed markers on said MSCs or MPCs.

Jone teaches regarding the limitations of various markers on the MSCs (MPCs) in claims 180, 181 and 183. In addition to Stro-1+ (Abstract; p3350, col.1, 2nd paragraph) cells further possess various markers including CD29, CD10, CD13 and were negative for CD34. Jones further teaches regarding expanding these cells in culture and clonal assays (entire article; p.3350, col.1, 3rd paragraph; col.2 2nd paragraph).

Bianco teaches CFU-F fraction derived bone marrow cells (which are enriched in Stro1+ cells) and their potential to differentiate into vascular cells (entire article abstract; p.181-184). Bianco further teaches localization and isolation of Stro-1 bright cells

fraction (p.182, co.1-2 bridging p.183-184) and teach that isolated stro-1 bright cells exhibit several endothelial markers (p.185, col.2, 2nd paragraph).

Dennis clearly teaches that a subset of marrow cells that express the Stro-1 antigen are capable of differentiatin into multiple mesecnhymal lineages including vascular smooth-muscle like phenotype etc (see Abstract).

Regarding claim limitations of using said MPCs or MSCs at various level of enrichment in claims 175-179 and 187-191 It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Further regarding various markers claimed for the MPCs/MSCs and their niche in a tissue (such as bone marrow peri-vascular niche etc) in claims 183-186, the Applicant should note Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir.1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)"

Thus it would have been obvious for one of ordinary skill in the art to incorporate into the method of promoting angiogenesis in an organ or tissue by administering MScs/MPC as taught by Chopp a with step of confirming the identity of MSCs and MPCs as Stro1+ or stro1+bright cells and enriching them as taught by Jones and/or Bianco administer an effective amounts of Stro1+bright cells enriched MPCs to induce neovascularization in a tissue as Dennis teaches that they can differentiate into vascular smooth muscle cell and endothelial cell phenotype.. One of ordinary skill in the art would have been motivated to use Stro-1+ cell enriched MPCs in order to induce angiogenesis or neovascualrization as it would promotes healing of the affected organ by relieving from ischemia by increasing blood circulation. One of ordinary skill in the art would have reasonable expectation of success in making and using enriched Stro 1+ or stro-1+ bright MPCs for inducing neovascualrization because the art teaches that it is routine to transplant MPCs to a tissue and obtain neovascularization, it is routine to make MPCs enriched in Stro1+ or stro-1+ bright cells and art further teaches regarding their potential to differentiate into vascular cells. Thus, the claimed invention was prima facie obvious.

Response to Applicants Arguments in the Response of 05/26/2009:

The Applicants amends the claims and argues that the instant invention is not obvious because Chopp reference which teaches neovascularization with bone marrow derived MPCs does not teach comprising or enriched with Stro1+ cells and the Applicant argues that Jones reference that teaches Stro1+ cell enrichment does not teach neovascularization.

The Applicants arguments are however found not persuasive. The Applicant first should note that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested

to those of ordinary skill in the art." In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). Prior art clearly teaches that CFU-F fraction of BM cells clearly are enriched in cell comprising Stro 1+ cells. Show whoever uses BM derived CFU-F fraction of cells clearly inherently uses MPCs that comprise Stro1+ cells. Further the supporting art of Jones clearly teaches enrichment of Stro 1+cells in BM derived MPCs. Thus the above references make the invention obvious when combined in the light further knowledge available in the prior art. For example, the instant rejection promulgated above brings in two new references, that of Bianco and Denis bothof which teach vascular differentiation potential of stro1+ fraction of BM derived MPCs and further an enrichment of Stro1+bright cell fraction. Hence, the invention as claimed was obvious to one of skill in the art at the time of instant invention.

Conclusion

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.,* may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or

proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/
Primary Examiner, Art Unit 1633